	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	2	6388054.pn.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 10:33			0
2	BRS	L3	1	wo-200011022-$.did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:14			0
3	BRS	L4	2	pya-bip-atmp	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:16			0
4	BRS	L5	36937	(tumor adj growth) or apoptosis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:18			0
5	BRS	L6	0	4 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:18			0
6	BRS	L7	2	4 and 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:22			0
7	BRS	L8	536	stewart adj john.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:22			0
8	BRS	L9	32	chan adj daniel.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
9	BRS	L10	11	gera adj lajos.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
10	BRS	L11	2	york adj eunice.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
11	BRS	L12	14	bunn adj paul.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
12	BRS	L13	572	8 or 9 or 10 or 11 or 12	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0
13	BRS	L14	2	4 and 13	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0

=> d his

(FILE 'HOME' ENTERED AT 12:27:37 ON 23 OCT 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
12:27:59 ON 23 OCT 2004

L1 0 S PYA-BIP-ATMP
L2 0 S ACRYLOYL (P) BIPHENYLALANINE (P) PIPERIDINE
L3 829698 S ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS
L4 0 S M296
L5 18825 S STEWART J?/AU
L6 5547 S CHAN D?/AU
L7 448 S YORK E?/AU
L8 1503 S BUNN P?/AU
L9 25899 S L5 OR L6 OR L7 OR L8
L10 447 S L9 AND L3
L11 57942 S SMALL CELL LUNG CANCER
L12 15223 S BRADYKININ (P) ANTAGONIST
L13 13039 S SCLC
L14 61690 S L11 OR L13
L15 93 S L12 (P) L14
L16 25 S L10 AND L15
L17 14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

=> log y

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FILE 'MEDLINE' ENTERED AT 12:27:59 ON 23 OCT 2004

FILE 'CAPLUS' ENTERED AT 12:27:59 ON 23 OCT 2004
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FILE 'AGRICOLA' ENTERED AT 12:27:59 ON 23 OCT 2004

=> s pya-bip-atmp
L1             0 PYA-BIP-ATMP

=> s acryloyl (p) biphenylalanine (p) piperidine
L2             0 ACRYLOYL (P) BIPHENYLALANINE (P) PIPERIDINE

=> s antitumor or (tumor growth) or apoptosis
L3        829698 ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS

=> s m296
L4             0 M296

=> s stewart j?/au
L5         18825 STEWART J?/AU

=> s chan d?/au
L6          5547 CHAN D?/AU

=> s york e?/au
L7           448 YORK E?/AU

=> s bunn p?/au
L8          1503 BUNN P?/AU

=> s l5 or l6 or l7 or l8
L9         25899 L5 OR L6 OR L7 OR L8

=> s l9 and l3
L10          447 L9 AND L3

=> s small cell lung cancer
   5 FILES SEARCHED...
L11        57942 SMALL CELL LUNG CANCER

=> s bradykinin (p) antagonist
L12        15223 BRADYKININ (P) ANTAGONIST

=> s sclc
L13        13039 SCLC

=> s l11 or l13
L14        61690 L11 OR L13

=> s l12 (p) l14
L15           93 L12 (P) L14

=> s l10 and l15
L16           25 L10 AND L15

=> duplicate remove l16
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L16
L17            14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

=> d l17 1-14 ibib abs

L17  ANSWER 1 OF 14     MEDLINE on STN                    DUPLICATE 1
```

ACCESSION NUMBER: 2002215358 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11930011
TITLE: Bradykinin antagonist dimer, CU201, inhibits the growth of human lung cancer cell lines by a "biased agonist" mechanism.
AUTHOR: ***Chan Daniel*** ; Gera Lajos; ***Stewart John*** ; Helfrich Barbara; Verella-Garcia Marileila; Johnson Gary; Baron Anna; Yang Jie; Puck Theodore; ***Bunn Paul Jr***
CORPORATE SOURCE: Lung Cancer Program, University of Colorado Cancer Center, Denver, CO 80262, USA.. Dan.Chan@UCHSC.edu
CONTRACT NUMBER: CA 46934 (NCI)
CA 58187 (NCI)
CA78154-01 (NCI)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 Apr 2) 99 (7) 4608-13.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020416
Last Updated on STN: 20020426
Entered Medline: 20020425

AB All small cell (***SCLCs***) and many non- ***small*** ***cell*** ***lung*** ***cancers*** (NSCLCs) have neuroendocrine features including production of neuropeptides and cell surface receptors creating autocrine and paracrine growth loops. Neuropeptides bind to a family of 7-transmembrane receptors and activate heterotrimeric G proteins consisting of G(alphaq) and G(alpha12,13). Substance P derivatives (SPDs) induced ***apoptosis*** and inhibited growth of lung cancer cells by discoordinately inhibiting G(alphaq) and stimulating G(alpha12,13). However, these SPDs had low potency and short half-lives. In this report we show that a ***bradykinin*** ***antagonist*** dimer, CU201, inhibited the growth of ***SCLC*** and NSCLC cell lines with or without multidrug-resistant proteins and was 10-fold more potent with a longer plasma half-life than SPDs. ***Bradykinin*** agonists in either monomeric or dimeric form and monomeric ***bradykinin*** ***antagonist*** have no effect on lung cancer cell growth. The dimeric linking moiety of the two molecules was created, requiring a sufficient number of carbon chains to provide critical spacing between the two ***antagonists*** . CU201 inhibited intracellular Ca2+ release in response to ***bradykinin*** , indicating blockage of the G(alphaq) signal, and stimulated c-Jun kinases, indicating stimulation of the G(alpha12,13) pathway. CU201-induced ***apoptosis*** was preceded by unique changes in apparent nuclear DNA binding and by c-Jun kinase and caspase-3 activation. At the concentration at which CU201 inhibited the growth of the cancer cells, it had no effect on the growth of normal lung cells in vitro. CU201 and similar compounds offer hope of becoming a new form of targeted therapy for tumors with neuroendocrine properties.

L17 ANSWER 2 OF 14 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002276331 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12006549
TITLE: Bradykinin antagonist dimer, CU201, inhibits the growth of human lung cancer cell lines in vitro and in vivo and produces synergistic growth inhibition in combination with other ***antitumor*** agents.
AUTHOR: ***Chan Daniel C*** ; Gera Lajos; ***Stewart John M*** ; Helfrich Barbara; Zhao Tom Limin; Feng Wan Yong; Chan Kenneth K; Covey Joseph M; ***Bunn Paul A Jr***
CORPORATE SOURCE: Lung Cancer Program of the University of Colorado Cancer Center, University of Colorado Health Sciences Center, Denver 80262, USA.. Dan.Chan@UCHSC.edu
CONTRACT NUMBER: 1R43CA86581-01 (NCI)
CA 46934 (NCI)
CA58187 (NCI)
N01-CM07019 (NCI)
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2002 May) 8 (5) 1280-7.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210

NTRY DATE: Entered STN: 20020518
Last Updated on STN: 20021018
Entered Medline: 20021017

B ***Small*** ***cell*** ***lung*** ***cancers*** (***SCLCs***), many non- ***SCLCs*** , and other cancers have neuroendocrine features, including paracrineand autocrine growth stimulation by various neuropeptides. Interference with this pathway is an attractive target for novel therapies. We developed a novel ***bradykinin*** ***antagonist*** dimer, CU201 (B9870), that acts as a "biased agonist" for neuropeptides by blocking G(alphaq) signaling and activating G(alpha12,13) signaling. CU201 induced ***apoptosis*** and complete growth inhibition in various lung cancer and other cancer cell lines. CU201 was 10-fold more potent than substance P derivatives and was stable in serum for >7 days. In this study, we evaluated the ability of CU201 to produce additive or synergistic growth inhibition in combination with various ***antitumor*** agents used in lung cancer therapy. We found that CU201 produced additive or synergistic growth inhibition when combined with doxorubicin, etoposide, cisplatin, vinorelbine, and paclitaxel for ***SCLC*** lines and with paclitaxel and ZD1839, an epidermal growth factor receptor tyrosine kinase inhibitor, for non- ***SCLC*** cell lines. Pharmacokinetic parameters associated with the i.v. administration of CU201 were evaluated in normal mice, and the effects of CU201 on the growth of human lung cancer xenografts were evaluated in athymic nude mice. In CD2F1 mice given an i.v. bolus infusion of 5 mg/kg, the c(max) was 5773 ng/ml (5 microM), and the decay was biexponential. When fitted to a two-compartment model, the t(1/2alpha) was 14.4 min, and the t(1/2beta) was 44.3 h, indicating a long terminal half-life consistent with the prolonged in vitro effects. CU201 inhibited the growth of human lung cancers in athymic nude mice by the intratumoral, s.c., and i.p. routes at a dose of 5 mg/kg/day. This dose is >10-fold less than the dose of substance P derivatives used to inhibit ***SCLC*** xenografts in nude mice. We conclude that CU201 should undergo further preclinical toxicology studies in its development as a novel targeted therapy for the treatment of lung cancers with neuroendocrine features. These studies are in progress through the NCI RAID mechanism.

L17 ANSWER 3 OF 14 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002284334 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12025961
TITLE: Bradykinin-related compounds as new drugs for cancer and inflammation.
AUTHOR: ***Stewart John M*** ; Gera Lajos; ***Chan Daniel C*** ; ***Bunn Paul A Jr*** ; ***York Eunice J*** ; Simkeviciene Vitalija; Helfrich Barbara
CORPORATE SOURCE: Department of Biochemistry, University of Colorado School of Medicine, Denver 80262, USA.. john.stewart@uchsc.edu
CONTRACT NUMBER: CA78154 (NCI)
HL-26284 (NHLBI)
SOURCE: Canadian journal of physiology and pharmacology, (2002 Apr) 80 (4) 275-80.
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20021217
Entered Medline: 20021204

AB ***Bradykinin*** (BK) (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is an important growth factor for ***small*** - ***cell*** ***lung*** ***cancer*** (***SCLC***) and prostate cancer (PC). These cancers have cells of neuroendocrine origin and express receptors for a variety of neuropeptides. BK receptors are expressed on almost all lung cancer cell lines and on many PC cells. Our very potent BK ***antagonist*** B9430 (D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Oic-Arg) (Hyp, trans-4-hydroxy-L-proline; Igl, alpha-2-indanylglycine; Oic, octahydroindole-2-carboxylic acid) is a candidate anti-inflammatory drug but does not inhibit growth of ***SCLC*** or PC. When B9430 is dimerized by N-terminal cross-linking with a suberimide linker, the product B9870 is a potent growth inhibitor for ***SCLC*** both in vitro and in vivo in athymic nude mice. Daily i.p. injection at 5 mg x kg(-1) day(-1) beginning on day 8 after ***SCLC*** SHP-77 cell implantation gave 65% inhibition of ***tumor*** ***growth*** . B9870 stimulates ***apoptosis*** in ***SCLC*** by a novel "biased agonist" action. We have also developed new small mimetic ***antagonists*** . BKM-570 (F5C-OC2Y-Atmp) (F5C, pentafluorocinnamic

acid; OC2Y, O-2,6-dichlorobenzyl tyrosine; Atmp, 4-amino-2,2,6,6-tetramethylpiperidine) is very potent for inhibition of SHP-77 growth in nude mice. When injected daily i.p. at 5 mg x kg(-1), M-570 gave 90% suppression of ***tumor*** ***growth*** . M-570 is more potent than the well-known anticancer drug cisPlatin (60% inhibition) or the recently developed SU5416 (40% inhibition) in this model. M-570 also showed activity against various other cancer cell lines in vitro (***SCLC*** , non- ***SCLC*** , lung, prostate, colon, cervix) and inhibited growth of prostate cell line PC3 in nude mice. M-570 and related compounds evidently act in vivo through pathways other than BK receptors. These compounds have clinical potential for treatment of human lung and prostate cancers.

ANSWER 4 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
SION NUMBER: 2003:509828 CAPLUS
ENT NUMBER: 140:175313
: Structural modifications of highly potent bradykinin antagonists and their pharmacological consequences
R(S): ***Stewart, John M.*** ; Gera, Lajos; ***York,*** Eunice J.*** ; ***Chan, Daniel C.*** ; ***Bunn,*** Paul A., Jr.***
RATE SOURCE: Department of Biochemistry and Molecular Genetics, University of Colorado Medical School, Denver, CO, 80262, USA
E: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 945-946. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69EDWK; ISBN: 2-84254-048-4
ENT TYPE: Conference
AGE: English
Peptides and non-peptide ***bradykinin*** ***antagonists*** were synthesized, purified and characterized by std. methods. B-9430, which blocks both B2 and B1 receptors, is a truly outstanding ***antagonist*** . It is very potent, is totally resistant to enzymic degrdn. and is orally available. Use in this peptide of the new amino acid, .alpha.-(2-indanyl)glycine is important for conferring these remarkable properties. Higher potency was achieved with B-10206, which uses pentafluorophenylalanine and N-cycloheptylglycine. Potent and long-acting ***antagonists*** lacking the C-terminal Arg residue have been developed. Some of these are specific for B1 receptors (B-9958) or show combined B1-B2 ***antagonist*** activity (B-9858). The general desire for nonpeptide drugs has prompted the authors to develop small mol. BK ***antagonists*** . Among many compds., M-570 can be cited. While its anti-BK activity is not high, it has shown remarkable anticancer activity against small cell lung carcinoma (***SCLC***), both in vitro and in vivo. It is also active in vitro against prostate, colon, pancreas and breast cancer cell lines, as well as non- ***SCLC*** . The ***bradykinin*** ***antagonists*** stimulate ***apoptosis*** of cancer cells in vitro by a novel "biased agonist" mechanism; they stimulate one intracellular second-messenger pathway while inhibiting another. Taken together, these results strongly suggest that certain of these compds. should be developed as drugs for inflammation and cancers.
ENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 5 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
SION NUMBER: 2001:256049 BIOSIS
MENT NUMBER: PREV200100256049
: Bradykinin-related compounds as new drugs for lung cancer and inflammation.
OR(S): ***Stewart, John M.*** [Reprint author]; Gera, Lajos [Reprint author]; ***Chan, Daniel C.*** [Reprint author]; ***Bunn, Paul A., Jr.*** [Reprint author]; ***York, Eunice J.*** [Reprint author]; Helfrich, Barbara [Reprint author]
ORATE SOURCE: Univ. of Colorado Medical School, 4200 E. Ninth Ave., Denver, CO, 80262, USA
CE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A248. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001. Orlando, Florida, USA. March 31-April 04, 2001.
CODEN: FAJOEC. ISSN: 0892-6638.
MENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 19 Feb 2002

AB ***Bradykinin*** (BK: Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is an important growth factor for ***small*** ***cell*** ***lung*** ***cancer*** (***SCLC***). BK receptors are expressed on almost all lung cancer cell lines. Our very potent BK receptor ***antagonist*** B9430 (DArg-Arg-Pro-Hyp-Gly-Igl-Ser-DIgl-Oic-Arg) (Hyp: trans-4-hydroxy-L-proline, Igl: alpha-2-indanylglycine, Oic: octahydroindole-2-carboxylic acid) is a candidate antiinflammatory drug. When B9430 is dimerized by N-terminal crosslinking with suberimide, the product, B9870, is a potent growth inhibitor for ***SCLC*** strain SHP-77, both in vitro and in vivo in athymic nude mice. Daily i.p. injection at 5 mg/kg/day beginning on day 8 after SHP-77 cell implantation gave 70% inhibition of ***tumor*** ***growth*** . B9870 stimulates ***apoptosis*** in ***SCLC*** by a novel "biased agonist" action. We have also developed new small mimetic ***antagonists*** . M570 (F5C-OC2Y-Atmp) (F5C: pentafluorocinnamic acid, OC2Y: O-2,6-dichlorobenzyl tyrosine, Atmp: 4-amino-2,2,6,6-tetramethylpiperidine) is very potent for inhibition of SHP-77 growth in nude mice. When injected daily i.p. at 5 mg/kg, M570 gave 90% suppression of ***tumor*** ***growth*** . M570 is more potent than the well-known anti-cancer drug cisplatin (60% inhibition) or the recently developed SU5416 (40% inhibition) in this model. M570 also showed activity against various other cancer cell lines in vitro (***SCLC*** , non- ***SCLC*** lung, prostate, colon, cervix). M570 and related compounds evidently act through pathways other than BK receptors in vivo. These compounds have clinical potential for treatment of human lung cancers.

L17 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:894619 CAPLUS
DOCUMENT NUMBER: 134:216928
TITLE: Bradykinin antagonists: Anti-cancer drugs for the new millennium?
AUTHOR(S): ***Stewart, John M.*** ; Gera, Lajos; ***York,*** ***Eunice J.*** ; ***Chan, Daniel C.*** ; ***Bunn,*** ***Paul A., Jr.*** ; Helfrich, Barbara
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: Peptides for the New Millennium, Proceedings of the American Peptide Symposium, 16th, Minneapolis, MN, United States, June 26-July 1, 1999 (2000), Meeting Date 1999, 219-221. Editor(s): Fields, Gregg B.; Tam, James P.; Barany, George. Kluwer Academic Publishers: Dordrecht, Neth.
CODEN: 69ATHX
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The authors have shown that specialized bradykinin (BK) antagonist peptides and certain related smaller nonpeptide mols. can inhibit growth of certain lung and prostate cancers by stimulating ***apoptosis*** through a "biased agonist" mode of action. To this end the authors' investigated compds. related to the crit. C-terminal part of BK antagonist peptides and to the first reported nonpeptide BK antagonist, Dcg-2Nal-Aqu. BKM-226 was the first shortened peptide sequence dimer to show activity, and served as the "lead" compd. for further syntheses, which led to potent dimers such as BKM-516, BKM-790 and BKM-862. Among nonpeptides, potent compds. were found among both monomers (BKM-570) and dimers (BKM-620). Several of these compds. have been found to inhibit growth of tumors in vivo in athymic mice. Cancer cells were implanted s.c. in matrigel and allowed one week to establish. Mice were then injected i.p. daily with peptides at 5 mg/kg/day. The most potent compd. in vitro and in vivo found so far is BKM-638, which is active at 0.5 mg/kg/day against SHP-77. Peptide B9870 has been accepted for drug development.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:795997 CAPLUS
TITLE: New class of drug candidates for lung and prostate cancer.
AUTHOR(S): ***Stewart, John M.*** ; Gera, Lajos; ***York,*** ***Eunice J.*** ; ***Chan, Daniel C.*** ; ***Bunn,*** ***Paul A., Jr.***
CORPORATE SOURCE: Department of Biochemistry, University of Colorado

Medical School, Denver, CO, 80262, USA
OURCE: Abstracts of Papers, 220th ACS National Meeting, Washington, DC, United States, August 20-24, 2000 (2000) MEDI-001
CODEN: 69FZC3
UBLISHER: American Chemical Society
OCUMENT TYPE: Journal; Meeting Abstract
ANGUAGE: English
AB Biased agonists, which stimulate one second messenger pathway while inhibiting another, can stimulate ***apoptosis*** . Agents which have this property combined with anti-angiogenic action offer an exciting new approach to anti-cancer therapy. ***Bradykinin*** (BK) is an autocrine growth factor for prostate and lung cancers, notably small cell lung carcinoma (***SCLC***). Certain BK ***antagonists*** have been found to cause ***apoptosis*** of ***SCLC*** and prostate cancer cell lines in vitro and to inhibit growth of lung cancers implanted s.c. in athymic nude mice. ***Tumor*** ***growth*** in vivo can be completely inhibited without harmful effects to the host animals. Both effective peptides and non-peptides have been discovered. The peptides used are remarkable; they are totally enzyme-resistant and are orally available. Potent new compds. and mechanisms of action will be presented.

L17 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:288762 CAPLUS
OCUMENT NUMBER: 133:99226
ITLE: Dimers of bradykinin antagonists and their smaller molecular mimetics as potential anticancer drugs
AUTHOR(S): Gera, Lajos; ***Chan, Daniel C.*** ; Helfrich, Barbara; ***Bunn, Paul A., Jr.*** ; ***York,*** *** Eunice J.*** ; ***Stewart, John M.***
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics, University of Colorado Medical School, Denver, CO, 80262, USA
SOURCE: Peptides 1998, Proceedings of the European Peptide Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999), Meeting Date 1998, 850-851. Editor(s): Bajusz, Sandor; Hudecz, Ferenc. Akademiai Kiado: Budapest, Hung.
CODEN: 68WKAY
OCUMENT TYPE: Conference
LANGUAGE: English
AB The authors have developed a series of novel ***bradykinin*** (BK) ***antagonist*** dimers that are potent and selective in the growth inhibition of human ***small*** ***cell*** ***lung*** ***cancer*** (***SCLC***) cells in vitro and in vivo. In addn. to new BK analogs with shorter chains, some BK mimetics that exhibit impressive growth inhibitory properties are also reported here. Peptides and mimetics were prepd. using both conventional soln. phase or solid phase methods, purified by high performance liq. chromatog. (HPLC) and characterized by thin layer chromatog. (TLC), laser desorption mass spectrometry (LDMS) and amino acid anal. The tetrazolium colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) growth assay was used to monitor the potency and cytotoxicity of BK ***antagonists*** and mimetics in cell lines of human lung cancer. B9870-2 and some BK-related mimetic analogs (BKM-294, BKM-620 and BKM-622) may provide a novel approach for the development of clin. useful agents for the treatment of human lung cancer, which is the most fatal malignancy in the world.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:578886 CAPLUS
OCUMENT NUMBER: 132:666
ITLE: Dimers of bradykinin and substance P antagonists as potential anti-cancer drugs
AUTHOR(S): ***Stewart, J. M.*** ; Gera, L.; ***Chan, D.*** *** C.***
CORPORATE SOURCE: Department of Biochemistry, University of Colorado Medical School, Denver, CO, 80262, USA
SOURCE: Peptide Science: Present and Future, Proceedings of the International Peptide Symposium, 1st, Kyoto, Nov. 30-Dec. 5, 1997 (1999), Meeting Date 1997, 731-732. Editor(s): Shimonishi, Yasutsugu. Kluwer: Dordrecht, Neth.
CODEN: 68BYA5
OCUMENT TYPE: Conference
LANGUAGE: English

B The authors report dimers of ***bradykinin*** (BK) and substance P (SP) ***antagonists*** and heterodimers of SP and BK ***antagonists*** that are potent selectively cytotoxic agents for ***small*** ***cell*** ***lung*** ***cancer*** (***SCLC***). Although straight-chain analogs of SP and bombesin have shown toxicity against ***SCLC*** , none of the simple BK ***antagonists*** were toxic to cells, although they were very effective for inhibition of BK-evoked elevation of intracellular free calcium in ***SCLC*** cultures. Typical of this behavior is B-9430, a very potent 'third-generation' BK ***antagonist*** which is active against both B1 and B2 BK receptors and shows a long half-life in vivo. When this ***antagonist*** was crosslinked by suberimide at the N-terminus (B-201), potent cytotoxic activity was found. Dimers of 'first-generation' BK ***antagonists*** , such as CP-127, were introduced by investigators at Cortech , and while they are quite potent ***antagonists*** in many BK assays, were not cytotoxic. When the linker in CP-127 was moved to the N-terminus of the dimer (B-197) significant toxicity was found. Even dimers of the potent 'second-generation' Hoechst ***antagonist*** HOE-140 showed only low cytotoxicity against ***SCLC*** . Orosz et al. reported that a pseudopeptide substance P ***antagonist*** (B-237) was active against ***SCLC*** . The authors confirmed this activity, and found that neither a homodimer (B-240) nor a heterodimer of this peptide with the best BK ***antagonist*** (B-215) showed increased cytotoxicity. Certain of these new dimers are toxic to ***SCLC*** lines that show multidrug resistance phenotypes, testifying to the different mechanism of toxicity of these agents. Preliminary studies indicate that these new dimers act by stimulation of ***apoptosis*** in ***SCLC*** cells. Peptide dimer B-201 inhibited the growth of ***SCLC*** cell line SHP-77 when implanted s.c. in athymic (nude) mice. These dimers offer a new avenue for anti-cancer drug development.
EFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 1998:597936 CAPLUS
OCUMENT NUMBER: 130:567
ITLE: Potent, wide-spectrum, orally active bradykinin antagonists
UTHOR(S): ***Stewart, John M.*** ; Gera, Lajos; Whalley, Eric T.; Hanson, Wendy L.; Zuzack, John S.
ORPORATE SOURCE: Department of Biochemistry, University of Colorado School of Medicine, Denver, CO, 80262, USA
OURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 815-816. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
OCUMENT TYPE: Conference
ANGUAGE: English
B The authors examd. the structure-activity relationship of ***bradykinin*** ***antagonists*** contg. .alpha.-(2-indanyl)glycine (Igl). Compds. were examd. for activity on rat uterus, guinea pig ileum, rabbit aorta, B1 and B2 receptor binding, ***SCLC*** anticancer activity and anti-inflammatory activity. Acylation of the amino acid terminus of BK B2 ***antagonists*** with hydrophobic residues increases potency; acylation of B9430 with adamantaneacetic acid decreased B1 activity and gave a selective B2 ***antagonist*** . Analogs of B9430 lacking the C-terminal Arg and contg. added N-terminal basic residues are potent and persistent B1 ***antagonists*** . Monomeric compds. showed potent inhibition of calcium flux in ***SCLC*** cells, but are not cytotoxic. Some dimers, however, show potent and selectivity cytotoxicity for ***SCLC*** cultured cells; B9870 is very potent. Some of the ***bradykinin*** ***antagonists*** have potential in the treatment of chronic inflammation and in human lung cancer.
EFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 1998:597736 CAPLUS
OCUMENT NUMBER: 130:564
ITLE: New classes of bradykinin antagonists having anti-cancer and/or anti-inflammatory activity
UTHOR(S): Gera, Lajos; ***Stewart, John M.*** ; ***Chan,*** *** Dan*** ; Whalley, Eric T.; Zuzack, John S.; Burkard, Michael R.

ORPORATE SOURCE: Department of Biochemistry, University of Colorado School of Medicine, Denver, CO, 80262, USA
OURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 415-416. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
OCUMENT TYPE: Conference
ANGUAGE: English
B The authors prepd. examples of third generation ***bradykinin*** ***antagonists*** contg. .alpha.-(2-indanyl)glycine (Ig1) and examd. their B2 and B1 functional effects on guinea pig ileum and rat uterus (B2) and rabbit aorta (B1). The best full chain ***antagonists*** contg. Ig1 such as B9430 (D-Arg-Arg-Pro-Hyp-Gly-Ig1-Ser-D-Ig1-Ser-D--Oic-Arg) are extremely potent at both B1 and B2 receptors. They are orally active and have long persistence of action. Analogs of B9430 lacking the C-terminal Arg are potent and persistent B1 ***antagonists*** . The monomeric Ig1 ***antagonists*** inhibit ***bradykinin*** -evoked calcium flux in ***SCLC*** cells but are not cytotoxic. Some dimers of these show potent and selective cytotoxicity for ***SCLC*** cultured cells. Some of these new ***antagonists*** may have potential for development of drugs involving B1 and B2 receptors such as chronic inflammation or in situations where B1 receptors are involved. Dimeric ***antagonists*** may have potential in treatment of human lung cancers.
EFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN
CCESSION NUMBER: 1997:572651 CAPLUS
OCUMENT NUMBER: 127:243292
ITLE: Potent, long-acting bradykinin antagonists for a wide range of applications
UTHOR(S): ***Stewart, John M.*** ; Gera, Lajos; ***Chan,*** *** Daniel C.*** ; Whalley, Eric T.; Hanson, Wendy L.; Zuzack, John S.
ORPORATE SOURCE: Department of Biochemistry and Cancer Center, University of Colorado School of Medicine, Denver, CO, 80262, USA
OURCE: Canadian Journal of Physiology and Pharmacology (1997), 75(6), 719-724
CODEN: CJPPA3; ISSN: 0008-4212
UBLISHER: National Research Council of Canada
OCUMENT TYPE: Journal; General Review
ANGUAGE: English
B A review, with .apprx.30 refs. Actions of ***bradykinin*** (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg; BK) are mediated by constitutively expressed B2 receptors (which require the full BK peptide chain) and by B1 receptors (which require BK(1-8) as ligand) that are induced in inflammation. BK has many functions in normal and pathol. physiol., including initiation of most, if not all, inflammation. BK also evidently functions as an autocrine stimulant for growth of ***small*** ***cell*** ***lung*** ***cancer*** (***SCLC***). A new group of BK ***antagonists*** contg. the novel amino acid .alpha.-(2-indanyl)glycine (Igl) provides both broad-spectrum and selective ***antagonists*** for all these functions. As examples, D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Oic-Arg (B9430) is an extremely potent and long-acting ***antagonist*** of both B1 and B2 receptors, is stable against endogenous kininase enzymes, and is active in various in vivo models, including by intragastric administration. Acylation of B9430 with dehydroquinuclidine-2-carboxylic acid (Dhq) gives B9562, a highly selective B2 ***antagonist*** . In contrast, Lys-Lys-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Oic (B9858) is a highly potent and selective B1 ***antagonist*** . The dimer of B9430 linked at the amino terminus with suberimide is a potent selectively cytotoxic agent for ***SCLC*** cells. Results with these peptides suggest that a new generation of antiinflammatory and anticancer drugs may be at hand.

17 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
CCESSION NUMBER: 1997:231765 BIOSIS
OCUMENT NUMBER: PREV199799530968
ITLE: A new class of peptide antagonist dimers inhibits the growth of human lung cancer cells in vitro and in vivo.
UTHOR(S): ***Chan, D.*** [Reprint author]; Gera, L.; Helfrich, B.; Helm, K.; Whalley, E.; ***Bunn, P.*** ; ***Stewart, J.***

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RPORATE SOURCE:    Dep. Med., Univ. Colo. Cancer Cent., Denver, CO 80262, USA
URCE:              Proceedings of the American Association for Cancer Research
                   Annual Meeting, (1997) Vol. 38, No. 0, pp. 232-233.
                   Meeting Info.: Eighty-eighth Annual Meeting of the American
                   Association for Cancer Research. San Diego, California,
                   USA. April 12-16, 1997.
                   ISSN: 0197-016X.
CUMENT TYPE:       Conference; (Meeting)
                   Conference; Abstract; (Meeting Abstract)
NGUAGE:            English
TRY DATE:          Entered STN: 2 Jun 1997
                   Last Updated on STN: 9 Jul 1997

L7  ANSWER 14 OF 14  CAPLUS  COPYRIGHT 2004 ACS on STN
CESSION NUMBER:         1997:331460  CAPLUS
OCUMENT NUMBER:         127:44206
TLE:                    Potent, long-acting, orally-active bradykinin
                        antagonists for a wide range of applications
THOR(S):                  ***Stewart, John M.***  ; Gera, Lajos;   ***Chan,***
***                          Daniel C.***  ; Whalley, Eric T.; Hanson, Wendy L.;
                        Zuzack, John S.
ORPORATE SOURCE:        Department of Biochemistry, University of Colorado
                        Medical School, Denver, CO, 80262, USA
OURCE:                  Immunopharmacology (1997), 36(2,3), 167-172
                        CODEN: IMMUDP; ISSN: 0162-3109
UBLISHER:               Elsevier
OCUMENT TYPE:           Journal; General Review
ANGUAGE:                English
B   A review, with 40 refs.  Actions of   ***bradykinin***
    (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg; BK) are mediated by constitutively
    expressed B2 receptors, that require the full BK peptide chain, and by B1
    receptors, induced in inflammation, that use BK(1-8) as ligand.  In addn.
    to many physiol. and pathophysiol. functions, the growth factor activity
    of BK evidently allows it to act as an autocrine stimulant for
      ***small***     ***cell***     ***lung***     ***cancer***  .  A new group
    of BK   ***antagonists***   contg. the novel amino acid
    a-(2-indanyl)glycine provides extremely potent broad-spectrum as well as
    selective   ***antagonists***   for all these functions.
EFERENCE COUNT:         40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


> d his

    (FILE 'HOME' ENTERED AT 12:27:37 ON 23 OCT 2004)

    FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
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L1           0 S PYA-BIP-ATMP
L2           0 S ACRYLOYL (P) BIPHENYLALANINE (P) PIPERIDINE
L3      829698 S ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS
L4           0 S M296
L5       18825 S STEWART J?/AU
L6        5547 S CHAN D?/AU
L7         448 S YORK E?/AU
L8        1503 S BUNN P?/AU
L9       25899 S L5 OR L6 OR L7 OR L8
L10        447 S L9 AND L3
L11      57942 S SMALL CELL LUNG CANCER
L12      15223 S BRADYKININ (P) ANTAGONIST
L13      13039 S SCLC
L14      61690 S L11 OR L13
L15         93 S L12 (P) L14
L16         25 S L10 AND L15
L17         14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

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